SEQ ID NO:1 is found on page 13, lines 27-34, wherein it is stated that a nucleic acid is a colorectal cancer nucleic acid if the overall homology of the nucleic acid is... as high as 93 to 95 or 98%. Support for the second sample being taken from a second healthy individual, and a difference indicating that the first individual has colorectal cancer, is found on page 3, lines 22-26. Finally, support for the inclusion of bodily secretions in the comparison is found on page 35, lines 28-31. No new matter is added.

Support for the changes to claims 36 and 40 is found on page 35, lines 28-31, wherein it is stated that bodily secretions are useful samples to be probed for the presence of colorectal cancer proteins.

The Rejections

Rejection Under 35 U.S.C. §101

The Examiner has rejected claims 32-43 for allegedly lacking a credible or well-established utility.

The Examiner argues that the Applicants do not assert a credible or well established utility for their invention because, one of skill in the art would not accept the assertion that *any* quantifiable difference in gene expression between two tissue types is indicative of colorectal cancer, and further, that one of skill in the art would not accept that *any* of the nucleic acid molecules including SEQ ID NO:1 and those with 75% sequence identity thereto, could be used in practicing the claimed method with a reasonable degree of success.

According to the MPEP 2710(II)(C) "Any rejection based on lack of utility should include *a detailed explanation* why the claimed invention has no specific and substantial credible utility. Whenever possible *the Examiner should provide documentary evidence*... if documentary evidence is not available, *the Examiner should specifically explain the basis* for his or her factual conclusions" (emphasis added).

In the Office Action, the Examiner takes issue with applicants statement any quantifiable difference in expression can be used to detect cancer cells in the methods of the invention. In particular, the Examiner alleges that "one skilled in the art would not accept the assertion that any quantifiable difference in the level of expression of a gene is

indicative of colorectal cancer in the individual". Further, the Examiner states that "it would seem that a determination of the levels of expression of SEQ ID NO:1 in just any tissue and comparison thereof would not be useful for diagnosis of colorectal cancer because the change in expression (i.e. up-regulation) is less than 50% and the specification teaches that a difference in expression of at least 50% is ***preferable.***" (emphasis added)

Surprisingly, the Examiner presents no evidence to support his allegation that one of skill would not accept the assertions in the application. The Examiner simply states what appears to believe one of would or would not accept as indicative of cancer. As noted above, the Examiner must provide documentary evidence or a specific explanation of his reasoning. This the Examiner has not done. In the absence of some evidence or reasoning explaining why those of skill would not expect any quantifiable difference in expression useful in detecting cancer cells, the rejection is improper and should be withdrawn.

In an attempt to support the rejection the Examiner refers to another part of the application that states that the difference in expression is ***preferably*** greater than 50%. This statement in the specification is merely a reference to preferred embodiments of the invention and is irrelevant to whether one of skill would expect lower differences to be useful, as well. Thus, in so far as reasoning is presented in support of the allegation, it is flawed. The fact that the Applicants recite that a change of 50% is *preferred*, does not in any way imply that a change of 50% is *required.*

Contrary to the Examiner's assertion, the invention provides a specific, substantial and credible utility, namely detection of increased CBK8 expression levels in a sample comprising colorectal cells as a tool for the diagnosis of colorectal cancer. Such a discovery is obviously useful as it provides means, in addition to those already known in the art, for the diagnosis of colorectal cancer. As explained below, the rejection is improper because a showing required to support a rejection under 35 USC §101 cannot be made.

MPEP 2107.01(I) addresses what is required to establish a specific utility for a diagnostic invention. That section states that where an Applicant discloses "a specific biological activity and reasonably correlates that activity to a disease condition the disclosure is sufficient to identify a "specific utility" for the invention". Further, with regard to substantial utility, MPEP 2701.01(I) states that "an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition, defines a "real world" context of use in identifying potential candidates for preventive measures or for further monitoring".

MPEP 2107.02(III)(B) states that an assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

The Applicants have discovered that increased expression of CBK8 in a tissue sample comprising colorectal cells is correlated with the existence of colorectal cancer. As a result of their discovery they have invented a tool useful for the diagnosis of colorectal cancer.

The logic underlying the utility of the invention is that certain genes are differentially expressed in different physiological states, and that a particular physiological state can be identified by its gene expression profile or by components of that profile. This logic is well accepted in the art of cancer diagnosis. The Examiner has provided no evidence to the contrary on this point. Thus, the logic underlying the utility of the invention is not seriously flawed. On the contrary, the logic is an accepted basis for similar tests that are currently in use for the detection of many other cancerous conditions.

With regard to the second measure of credibility noted above, the facts presented are fully consistent with the logic upon which the assertion of utility is based. The data provided in Figures 3A-C show that CBK8 expression is significantly higher in colorectal cancer and metastatic colorectal cancer that it is in any other tissue of the body.

In conclusion, the Examiner has failed to make a proper showing to establish the claimed invention lacks utility. In the present application, the Applicants

have shown that CBK8 expression is up-regulated in primary and metastatic colorectal cancer samples. Therefore, the invention provides an assay for the diagnosis of colorectal cancer. The sample comprising colorectal cells could reasonably come from any tissue or any bodily secretion, because both primary and metastatic colorectal cancer show increased levels of CBK8 expression (*see e.g.* Figure 3A). Thus, the Applicants have provided a specific, substantial and credible utility for their invention. Reconsideration of the rejection under 35 U.S.C. §101, is respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph

I. Enablement

A. Unpredictability of the Art

The Examiner rejects the claims under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The Examiner argues that the molecular diagnosis of cancer is a highly unpredictable art and cites the studies of Rae *et al.* who examined the differential expression of genes in renal clear cell carcinoma. Rae *et al.* allegedly report that some genes are expressed at higher levels in tumor specimens than in normal specimens, while others were expressed at lower levels in tumor specimens than in normal specimens. However, because one of these genes, DD96, was not up-regulated, as had been expected based on the earlier reports, the Examiner concludes that in view of the teaching of Rae *et al.*, the field of molecular diagnostics is highly unpredictable, therefore one of skill in the art would not be able to practice the invention without undue experimentation.

As an initial matter, the Examiner must explain how the problems encountered during studies of Rae *et al.* (involving renal cell carcinoma) bear on the predictability of the art with respect to the Applicants' invention (directed to detection of colorectal cancer cells). In addition, evidence that some genes are universally overexpressed in certain cancer types is not evidence of unpredictability in the art. Indeed, the evidence in the present application demonstrates that there is variability of CBK8 gene expression among the many colorectal cancer cells testes. Thus, even though

a given marker may not be useful for diagnosing ***all*** colorectal cancers, it can still be used to detect cancers in which it ***is*** overexpressed.

The Examiner argues that the specification does not teach a clear distinction between the expression of SEQ ID NO:1 in colorectal cancer tissue versus many other tissues. The content of the Applicants' disclosure, combined with the knowledge of the art provides sufficient direction for one of skill in the art to practice the claimed invention.

The data presented in Figures 3A-C clearly show a distinction between the expression of SEQ ID NO:1 in colorectal cancer tissue versus many other tissues. Indeed, the data provided in Figures 3A-C show that CBK8 expression is significantly higher in colorectal cancer and metastatic colorectal cancer that it is in any other tissue of the body. The data show that out of a total of 76 measurements of colorectal cancer (both metastatic and primary), there are 67 instances in which CBK8 expression levels are higher in colorectal cancer and metastatic colorectal cancer than they are in the highest measurement taken for normal colon tissue. Thus, in more than 88% of the tested cells expression levels of CBK8 are higher in cancerous colorectal tissue than they are in normal colon tissue.

For other tissues expression levels of CBK8 are similar to expression levels in normal colon tissue. Thus, in most body tissues expression of CBK8 is significantly lower than it is in either primary or metastatic colorectal cancer. The most exceptional non-colorectal cancer tissue is colonic epithelial cell (CEP) tissue. In colonic epithelial cells CBK8 is, on average, expressed at a higher level than in most other body tissues. Nonetheless, 43 of the 76 measurements of CBK8 expression in primary and metastatic colorectal tissue reveal expression levels that are higher than the CBK8 expression observed in colonic epithelial cells. Thus, even in the very worst case, CBK8 is expressed at a higher level in 56% of colorectal cancer samples as compared with *any* other tissue in the body. Therefore, the Applicants show that increased CBK8 expression is a useful marker for the presence of colorectal cancer.

The Examiner further argues that the method does not exemplify a gene that is 75% identical to SEQ ID NO:1, and that the specification does not provide a threshold value that can be used to discriminate the individual that has primary or metastatic cancer from the individual who is disease free. As noted above, the claims have been amended to recite that the detected sequences are 95% identical to SEQ ID NO: 1. The claims therefore are directed to detection of sequences closely related to SEQ ID NO: 1, for example allelic variations that would be expected to occur in the human population. The Examiner has provided no reasoning or evidence that sequences within the scope of the pending claims would not be useful in the detection of cancer cells.

With regard to the required threshold level of expression, as discussed above, the specification specifically teaches that any quantifiable difference in expression can be used to detect cancer cells in the methods of the invention. As point out in the discussion above, the Examiner has not provided sufficient reasoning or evidence to call that teaching into question.

In conclusion, the Applicants have shown that CBK8 expression is significantly increased in individuals with colorectal cancer. Thus, they have provided an enabling disclosure to support their invention for the detection and diagnosis of colorectal cancer by detection of increased expression of CBK8.

B. How to Make and Use

The Examiner has also rejected the claims under 35 U.S.C. §112, first paragraph for alleged lack of utility. In this case the Examiner admits that there are differences in the expression levels of CBK8 in colorectal cancer and other tissues. However, the Examiner argues that the observed differential expression levels of CBK8 seen in Figures 3A-C could be due to epigenetic changes in late stage tumors. The Examiner asserts that if this were the case, the invention would not be useful because only early diagnosis is efficacious in treating disease. Moreover, the Examiner alleges that the high level of skill that must be exercised in order to dissect tumor tissue from possibly contaminating normal cells, precludes any useful application of the invention.

The Examiner also argues that the specification discloses nothing of the biologic role of the protein encoded by SEQ ID NO:1. Therefore, the Examiner concludes, it is unclear that the protein even has a role in the etiology and pathology of colorectal cancer.

The Applicants respectfully submit that none of these arguments are germane to the issue of utility and enablement of the Applicants' invention. Furthermore, the Examiner has not provided any evidence or reasoning to support his allegations.

The Examiner has also argued that the invention is not useful, and therefore not enabled because, as taught by Ward et al., not all markers can reliably be used for primary diagnosis. Thus, detection of the relative level of over-expression will not guarantee a definitive diagnosis of colorectal cancer. Furthermore, the Examiner argues that even if SEQ ID NO:1 were proved to be clinically useful, further research and validation would be required prior to the application of the newly described markers, and the predictive value would need to be confirmed in population trials.

The Applicants respectfully submit that enablement of the invention does not require that the invention detect every possible case of colorectal cancer. Indeed, the invention would be useful if its application was able to save even one life. Rather enablement requires that one teach how to make and use the invention. The Applicants have clearly taught how to diagnose colorectal cancer by detecting increased levels of CBK8 expression.

Furthermore, the fact that more experimentation will be necessary before the invention is marketed to the public does not constitute undue experimentation, and thus has no bearing on the enablement of the Applicants invention as filed.

According to MPEP 2107.01(III) the mere identification of a pharmacological activity for a compound that is relevant to an asserted use provides "immediate benefit to the public" and thus, satisfies the utility requirement. In fact, the Federal Circuit has reiterated that *therapeutic utility* under the patent laws *is not to be confused with the FDA with regard to safety and efficacy of drugs marketed in the United States* (emphasis added).

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott* [*v. Finney*], 34 F.3d 1058, 1063, 32USPQ2nd 1115, 1120 [(Fed.Cir. 1994)]. usefulness in patent law, and in particular in the context of pharmaceutical inventions necessarily includes the expectation of further research and development....

Thus, the fact that the Applicant is at a very early stage in the development of a therapeutic product or therapeutic regimen is not an inherent barrier to a claim of usefulness for the invention. In addition, the fact that the invention may be at an early stage of development is not an appropriate basis for rejecting the claims for lack of enablement. Indeed, according to MPEP 2164.01 the test of enablement is whether one skilled in the art could make or use the invention... without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

Thus, the Applicants' useful invention is supported by an enabling disclosure. The Applicants respectfully request reconsideration of the enablement rejection under 35 U.S.C. §112, first paragraph.

Written Description

The Examiner rejects claims 32-40 and 42-43 under 35 U.S.C.§112, first paragraph for allegedly failing to convey that the Applicants had possession of the invention at the time the application was filed.

Claims 32 has been amended to recite "identical to a nucleic acid sequence 95% identical to SEQ ID NO:1". This amendment should correct the defects in the specification, to which the Examiner objected.

The Examiner had concluded that there was no evidence that a reduction to practice had occurred by the time the application was filed. The Applicants point out that, as shown above, the invention has a specific, substantial and credible utility. The specific, substantial, and credible utility is supported by an enabling disclosure. Therefore, according to MPEP 2138.05 a constructive reduction to practice occurred at

the time the application was filed. The Applicants therefore respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 32- 43 under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter that the Applicant regards as the invention.

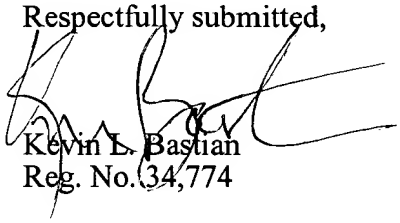
The Examiner rejects claims 32-43 because claim 32 allegedly fails to recite a positive correlation step that relates back to the preamble of the claim. The Examiner also rejects claims 32-43 for reciting "first sample" and "second sample" without indicating from where such samples originated.

The Applicants have addressed the Examiner's concerns with appropriate claim amendments. The Applicants thank the Examiner for kindly suggesting amendments that would obviate the rejections, and respectfully request reconsideration of the rejection under 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 9, lines 33-34 carrying over to page 10, lines 1-9:

In a preferred embodiment, colorectal cancer sequences are those that are up-regulated in colorectal cancer; that is, the expression of these genes is higher in colorectal carcinoma as compared to normal colon tissue. "Up-regulation" as used herein means at least about a 50% increase, preferably a two-fold change, more preferably at least about a three fold change, with at least about five-fold or higher being preferred. All accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. GenBank is known in the art, see, e.g., Benson, DA, et al., Nucleic Acids Research 26:1-7 (1998) [and http://www.ncbi.nlm.nih.gov/]. In addition, these genes were found to be expressed in a limited amount or not at all in bladder, bone marrow, brain, colon, fibroblasts, heart, kidney, liver, lung, muscle, pancreas, prostate, skin, small intestine, spleen, stomach and testes.

Page 14, lines 22-35:

Another example of a useful algorithm is the BLAST algorithm, described in Altschul et al., J. Mol. Biol. 215, 403-410, (1990) and Karlin et al., PNAS USA 90:5873-5787 (1993). A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul et al., Methods in Enzymology, 266: 460-480 (1996)[[http://blast.wustl/edu/blast/ READ.html]]. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span =1, overlap fraction = 0.125, word threshold (T) = 11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity. A % amino acid

sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-Blast-2 to maximize the alignment score are ignored).

IN THE CLAIMS:

32. (Amended) A method of diagnosing colorectal cancer comprising:

a) determining the expression of a [gene] nucleic acid sequence at least [75] 95% identical to SEQ ID NO:1 in a first sample comprising colorectal cancer cells from a first individual; and

(b) comparing the expression of said [gene] nucleic acid sequence in the first sample to expression of said [gene] nucleic acid sequence in a second sample taken from either normal colon tissue of said first individual or from normal colon tissue, or a bodily secretion of a second unaffected individual;

wherein [said comparison is used to diagnose colorectal cancer] a difference between the expression in the first sample and the expression in the second sample indicates that the first individual has colorectal cancer.